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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,577	03/23/2001	Brittan L. Pasloske	AMBI:054US/MBW	7249

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EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/815,577	Applicant(s) Pasloske et al.	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE --3-- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

[X] Responsive to communication(s) filed on -06/03/02 (amdt B & declaration) & 10/04/01 (IDS)-.

[] This action is **FINAL.**

[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

[X] Claims —54, 56-73 and 75-120— are pending in the application. Claims -54 and 74- have been cancelled. Of the above claim(s) —[]— is/are withdrawn from consideration.

[] Claim(s) —[]— is/are allowed.

[X] Claims —54, 56-73 and 75-120— are rejected.

[] Claim(s) —[]— is/are objected to.

[] Claim(s) —[]— are subject to restriction or election requirement.

Application Papers

[] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[X] The proposed drawings, filed on -03/23/01- are [X] approved [] disapproved.

[] The drawing(s) filed on -[]- is/are objected to by the Examiner.

[] The specification is objected to by the Examiner.

[] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

[X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).

[X] All [] Some* [] None of the CERTIFIED copies of the priority documents have been

[] received.

[] received in Application No. (Series Code/Serial Number) -[]-.

[X] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: -[]-.

Attachment(s)

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). —06—

[X] Notice of Reference(s) Cited, PTO-892 (Update)

[] Notice of Draftsperson's Patent Drawing Review, PTO-948

[] Interview Summary, PTO-413

[] Notice of Informal Patent Application, PTO-152

[] Other: -[]-.

Claims **55 and 74** have been cancelled, claims **54, 56-57, 73, 75-76, 80 and 86-87** have been amended, and new claims **88-120** have been added as per the amendment filed June 3, 2002. An Information Disclosure Statement (IDS) filed October 4, 2001 has been received with all listed reference and made of record. A declaration filed under 37 C.F.R. §1.132 and signed by declarant Iverson has also been received and has been considered in the preparation of the instant Office action.

Claims **54, 56-73 and 75-120** remain in the case.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **54, 57, 61-72 and 88-120** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-25 and 32-44** of copending Application No. **09/160,284**. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims may be read to be directed to the deactivation of ribonuclease enzymatic activity by contacting a sample thought to be contaminated with ribonuclease with a disulfide-forming reducing agent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed June 3, 2002 have been fully considered but they are not persuasive.

Applicant has acknowledged the validity of the instant grounds of rejection but has yet to submit an acceptable terminal disclaimer.

Claims **54, 56-60, 69-73, 75-78, 80-83, 85-103 and 111-120** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In the instant disclosure and in claims not listed in this rejection (e.g. claims **61-68**) applicant has listed specific reducing agents limited to thiol (-SH) containing compounds and in independent claims has relied on the term "reducing agent." The compounds which are not thiol containing agents but are "reducing agents" and which are not enabled herein is substantial. Therefore, the instant written description fails to

provide adequate support for the breadth of claims wherein the non-thiol reducing agents are included. Limitation to thiol containing reducing agents is respectfully requested.

Applicant's arguments filed June 3, 2002 have been fully considered but they are not persuasive.

Applicant is referred to the response following the next grounds of rejection.

Claims **54, 56-73, 75-79, 91, 97, 104-114 and 118-120** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In claims **54, 56-73, 75-79, 91, 97, 104-114 and 118-120** there is an implicit assumption that the mixture of an RNAse and RNA can be treated with a chemical reducing agent and that said reagent will selectively act on the RNAse without interference from the RNA present. Applicant is referred to PTO-892 reference "**W**" (**Murthy et al.**) at p. 347, column 1, first full paragraph, wherein it is stated that " .. the presence of RNA during [DTT] pretreatment [of the enzyme] was found to resist such a change, implying substrate stabilization of the RNAse BS-1 in the dimeric state with lower inhibitor-sensitivity, or insensitivity to it." In the same reference at p. 344, column 2, the 10 lines above Figure 1 disclose that DTT is mixed with an RNAse/RNA mixture at 37 degrees. And in Figures 4 and 5, the influence of the concentration of RNA on RNAse inactivation is disclosed. Because the instant disclosure does not appear to present a clear and cogent explanation of how applicant's have

overcome the problem of inhibitor induced RNAse insensitivity to a thiol reducing agent disclosed in the noted prior art disclosure, examiner concludes that the instant claims are at a minimum lacking in enablement for exemplifications wherein as noted in Murthy et al. the inhibitor has no effect on the enzyme because of the interaction of the enzyme with the RNA substrate. In addition, the disclosure of Murthy et al. at p. 345, Figure 3, and associated explanatory text teaches that the RNAse "BS-1" retains some to all of its enzymatic activity after reduction of the RNAse with DTT at 37°C either in the presence of an RNAse inhibitor or in the absence thereof. Therefore, it is clear that applicant's generic claims wherein the specific RNAse's to be inactivated have not been specified lack proper enabling support; i.e. not all RNAse's are effectively inhibited by the reducing agents of the instant claimed process. Therefore, in light of the Murthy et al. disclosure, applicant is respectfully requested to limit the scope of the instant claims to the specific embodiments.

Furthermore, the disclosure of the **Khesin et al.** reference (PTO-892 ref. **Y**) directly contradicts the assumption that the action of reducing agents including "DTT" and the like on ribonucleases always reduces ribonuclease activity, suggesting that limitations on claim scope are essential in order to take this reference into account.

Applicant's arguments filed June 3, 2002 have been fully considered but they are not persuasive.

Applicant argues that the rejection of record "certainly provides no evidence or reasoning upon which one could base any rejection under 35 U. S.C. §112, first paragraph under a [standard of] preponderance of the evidence." Examiner respectfully disagrees, noting in particular that both the Khesin and Murthy references provide ample factual basis to

question applicant's apparently absolute assertion that **all** RNAases will be effectively inactivated by applicant's claimed process conditions. In fact, Khesin discloses it its abstract that in at least one case an RNAase is observed to have enhanced activity following contact with the reducing agent DTT. Likewise in Murthy at page 344, column 2, the treatment of RNAase BS-1 with DTT was carried out at 0°C, 10°C and 37°C, and in either the presence or the absence of "inhibitor" (assumed to be "human placental RNAase inhibitor" mentioned under **Materials**) did not show complete loss of activity. Therefore, appropriate facts and reasoning sufficient to support the instant grounds of rejection have been supplied as required.

Applicant argues that the term "reducing agent" is adequately described in the disclosure. Examiner respectfully disagrees, noting at page 6, lines 23-24, that applicant has stated that the "[p]resently preferred reducing agents are those comprising DTT, ß-mercaptoethanol, cysteine or dithioerithritol (correct spelling is --dithioerythritol--)," a definition which leaves the door wide open to add any other chemical compound or reagent combination without limit, including obviously unenabled and inoperative embodiments such as $LiAlH_4$ and $H_2(g)$ plus Platinum black. The Iverson declaration at paragraph 8 states that [t]he inactivations of RNAase A, RNAase 1, and RNAase T1 disclosed in the specification are examples that prove that the methods work.". Examiner agrees, but with the proviso that only the examples provided have been shown to work. Iverson at paragraph 9 than further asserts that the prospective disclosures of the specification justify extrapolation of the methods known to work in three cases to all cases, and buttresses this in paragraph 10 by asserting that only routine experimentation is needed to determine which other RNAases are full inactivated by the claimed method.

Mssr. Iverson at paragraph 14 then asserts with reference to Figure 1 of Murthy et al. that "there was no inhibition of the ribonucleases studied when they were exposed to DTT without human placental ribonuclease inhibitor."(emphasis added) Examiner agrees, and finds this statement to be in support of Examiner's view that Murthy et al. has disclosed a finding that at least one RNAase (RNAase BS-1) retains activity after exposure to DTT even when flooded with a known inhibitor. However, Mssr. Iverson then appears to assert that Murthy et al. is totally lacking in credibility because in declarant's view Murthy et al. teaches that "DTT cannot be used [to] inactivate ribonucleases." In response Examiner notes that the instant rejection of record does not question the credibility of any prior art reference nor the credibility of the instant examples. Examiner reinterates that the rejection of record stands for the proposition that applicant has found a process that inactivates certain ribonucleases, but not all ribonucleases.

Mssr. Iverson in the last sentence of paragraph 15 concludes that Murthy et al. ... does not teach or suggest the use of a "combination of a reducing agent and heat to inactivate ribonucleases." Examiner agrees, noting that Murthy and Khesin both teach the that contacting certain RNAases with a reducing agent, with or without heat, does not inactivate said ribonucleases. In light of Mssr. Iverson's admission, Examiner does not understand why a previous offer in the parent case suggesting narrower claims did not produce agreement.

In summary, Examiner respectfully disagrees with the substance of applicant and declarant Iverson's cited arguments, and argues that the instant claims remain inadequately enabled because of excessive breadth and the failure of the disclosure to provide any guidance concerning how one of ordinary skill would be able to determine using a simple test

which RNAses are likely to be completely inactivated and which are not. In the absence of such guidance examiner asserts that the instant claims violate the judicial guidance found in *In re Gardner* which teaches that it is well known and established that the "law requires that disclosure in an application shall inform those skilled in the art how to use appellant's alleged discovery, not how to find out how to use it for themselves." *In re Gardner et al.*, 166 USPQ 138 (CCPA 1970). In light of the prior art based, herein established lack of predictability in this art, and the consequential need for undue experimentation, applicant is again respectfully requested to limit the scope of the instant claims to the specific embodiments or to take other appropriate action.

Claims **54, 56-57, 61-72, 75-76, 86-87, 91-96, 99-103 and 115-117** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **54**, the term "method of treating an extract of a cell comprising" is incomplete because the purpose of the method has still not been completely supplied; i.e. the claim begs the amended question "method of doing what to accomplishing what?". See also claims **56-57, 61-72 and 91.**

Applicant's arguments with respect to claims **54-87** have been considered but are moot in view of the new grounds of rejection required by applicant's amendment.

In claims **86 and 87** the term "a ribonuclease resistant RNA standard" is generic terminology which fails to provide a complete definition of the chemical identity or identities substance or mixture of substances being referred to.

Applicant's arguments with respect to claims **54-87** have been considered but are moot in view of the new grounds of rejection required by applicant's amendment.

In new claims **91-96 and 99-103** the term "at least one ribonuclease" lacks antecedent basis in claim **54**. See also claims **115-117** which similarly lack antecedent basis in claim **73**.

Applicant's arguments with respect to claims **54-87** have been considered but are moot in view of the new grounds of rejection required by applicant's amendment.

In claim **120** the term "further defined" is technically incorrect because the claim lacks proper antecedent basis in claim **73**. Did applicant intend the term to read -- further comprising --? See again claim **56-58, 75-76 and 81**.

Applicant's arguments with respect to claims **54-87** have been considered but are moot in view of the new grounds of rejection required by applicant's amendment.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims **80-81 and 83-85 are** rejected under 35 U.S.C. §102(**b**) as being anticipated by **Murthy et al.** (PTO-892 ref. **W**).

Applicant is referred to PTO-892 reference "**W**" (Murthy et al.) at p. 347, column 1, firs full paragraph, wherein it is stated that " .. the presence of RNA during [DTT] pretreatment [of the enzyme] was found to resist such a change, implying substrate stabilization of the RNAse BS-1 in the dimeric state with lower inhibitor-sensitivity, or insensitivity to it." In the same reference at p. 344, column 2, the 10 lines above Figure 1 disclose that DTT is mixed with an RNAse/RNA mixture at 37 degrees. Therefore this reference anticipates the combinations of compositions of the noted claims.

Applicant's arguments with respect to claims **54-87** have been considered but are moot in view of the new grounds of rejection.

Claims **80-81 and 83-85 are** rejected under 35 U.S.C. §102(**b**) as being anticipated by **Boshes et al.** (PTO-892 ref. **U**).

Boshes et al. discloses at p. 478, column 2, under "Extraction Procedures" a mixture of DTT and Tris-HCl buffer. Additionally Boshes et al. discloses at page 478, column 1, following "BULK RNA" that "DTT as added to all solutions in place of 0.001 % sodium heparin as a ribonuclease inhibitor." Therefore this reference anticipates the combinations of compositions of the noted claims.

Applicant's arguments with respect to claims **54-87** have been considered but are moot in view of the new grounds of rejection.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **54, 56-57, 61-72 and 97** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Boshes et al.** (PTO-892 ref. **U**) in view of **Cleland** (PTO-892 ref. **V**).

The instant claims are directed to all processes wherein cells or extracts thereof are contacted with a reducing agent without heating, at an undefined level of heating, or optionally at one of two defined levels of heating, are applied.

Boshes et al. at page 485, at the bottom of column 2, discloses that DTT and ß-mercaptoethanol are both capable of reducing one or more of the RNAse enzymes found in extracts of *drosophila* larvae; i.e. specifically identified as an inhibitor of RNAase activity by chemical reduction thereof.

Cleland discloses in its abstract and at page 480, column 1 et seq, that there are numerous reducing agents with substantial equivalence to DTT, including DET, cysteine, and ß-mercaptoethanol. This reference does disclose the utility of DTT in maintaining coenzyme A in its monomeric form, but does not disclose the use of DTT or any other sulfide reducing agent to inactivate a ribonuclease.

The cited portion of the Boshes et al. reference is clearly directed to the use of DTT for the reductive inhibition of *drosophila* ribonuclease(s) with resultant cessation of RNAase activity. Cleland is directed to DTT and related compounds as chemical reducing agents

useful in the cleavage of biologically important disulfide linkages, an overlap with the Boshes references which is deemed to be an adequate basis to motivate the combination of these two references and thereby expand the scope of the prior art disclosure to cover a larger number of thiol reducing agents.

Therefore, the instant claimed method of stabilizing mixtures of RNA and RNAse's by contacting same with a reducing agent like DTT would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments with respect to claims **54-87** have been considered but are moot in view of the new grounds of rejection.

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Johann Richter, can be reached at (703)-308-4532.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

LECrane:lec
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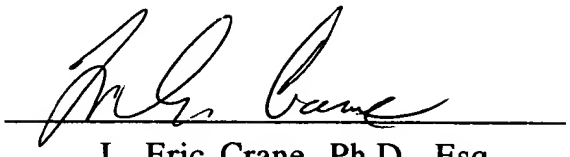

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